A Randomized, Double-Blind, Placebo Controlled Dose Ranging Study of Auxora in Patients with Acute Pancreatitis (AP) and Accompanying Systemic Inflammatory Response Syndrome (SIRS) - CARPO (NCT0468106)

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Acute Pancreatitis (AP) is a Complex Inflammatory Syndrome with No Approved Therapies and Significant Unmet Needs

AP can be life threatening and imparts a significant disease burden for patients[1]

20-30% of all AP patients experience pancreatic necrosis[1]

Persistent organ failure may occur in up to **25%** of AP patients[1]

Presence of organ failure increases the risk of mortality to as much as **50%**[1]

AP is among the leading causes of GI-related hospitalizations representing a significant economic burden[2]

300K+ annual hospitalizations in the US[2]

Resulting in **> 1 million** patient days in hospital per year[2]

Costing **> $3 billion** dollars annually in the US[2]

1) Bruen et al., Auxora for the Treatment of Patients With Acute Pancreatitis and Accompanying Systemic Inflammatory Response Syndrome, Pancreas, 2021, 537 – 543, 2) Peery et al., Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018, Gastroenterology, 2019, 254-272

Overactive Calcium Release-Activated Calcium (CRAC) Channels Contribute to AP; Auxora, a CRAC Channel Inhibitor, Targets Multiple Pathways

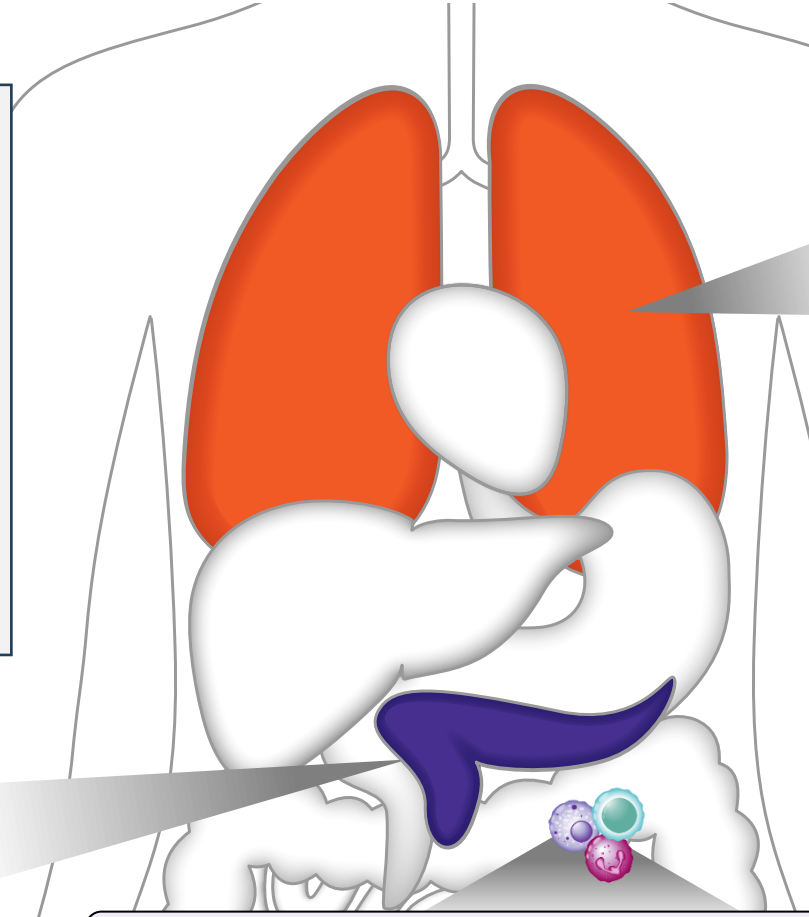
Gallstones and excessive alcohol use are the most common causes of AP

Bile and fatty acid esters cause excessive release of Ca^{2+} in pancreatic acinar cells

CRAC channels are overactive, causing cellular Ca^{2+} overload and dysfunction

Acinar cell autodigestion and necrosis; Ductal cell dysfunction and stellate cell activation

Auxora



Cascade of pro-inflammatory mediators
(T Cells, Neutrophils, Macrophages)

Auxora

Acute lung injury and multiple organ failure

Auxora

Systemic Inflammatory Response Syndrome (SIRS)

1) Peng S, Ke L, Li W., ORAI1 CRAC Channgel in Immune Cell is a Therapeutic Target for Pancreatitis-Associated Acute Lung Injury. 2023; 2) CalciMedica Inc. CRACing inflammatory disease. 2021.

Initial Signs of Efficacy for Auxora in AP with SIRS in a Phase 2a Trial Prompted Further Development in a Blinded, Randomized Control Trial

Phase 2a Outcomes[1]

Evidence from an open-label trial in patients with AP plus SIRs and hypoxemia sponsored by CalciMedica demonstrated Auxora plus standard of care (SOC) compared with SOC alone:

- ✓ Reduced the median hospital stay
- ✓ Reduced disease severity in patients presenting with moderate or severe AP
- ✓ Reduced incidence of persistent SIRS
- ✓ Rapidly restored appetite and tolerance of solid food
- ✓ Generally well-tolerated

Goals for Phase 2b CARPO Trial in AP Patients with SIRS

Learnings from previous development informed CalciMedica's goals for the Ph2b CARPO trial:

- Demonstrate ***dose response*** and biological activity across multiple primary and secondary endpoints including the pre-defined ***hyper-inflammatory patient population*** (high hematocrit)
- Demonstrate ***impact on organ failure***, especially in the lung, which is a significant risk for AP patients presenting with SIRS
- Demonstrate ***reduction in duration of hospital stays*** for patients
- Continued ***tolerability*** of Auxora
- Understand Auxora's potential benefits to patients to ***design a Phase 3 trial*** for discussion with the FDA

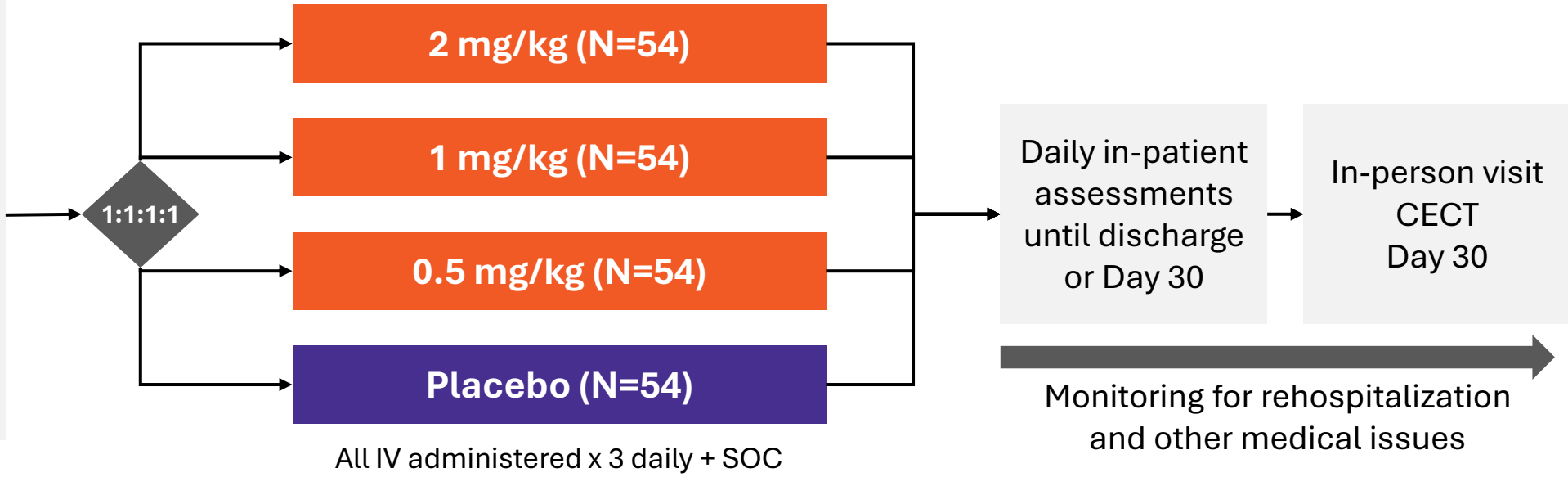
1) Bruen et al., Auxora for the Treatment of Patients With Acute Pancreatitis and Accompanying Systemic Inflammatory Response Syndrome, Pancreas, 2021, 537 – 543.

The Phase 2b CARPO Trial was Designed to Evaluate Dose Response on Key Outcomes for AP Patients with SIRS

Primary Objective: Dose Response on Primary and Secondary Endpoints

SCREENING
- Assess for SIRS
- Inclusion criteria
  - High hematocrit and/or
  - Peripancreatic fluid and/or
  - Abdominal guarding or tenderness
- Baseline CECT

N = 216



Primary Endpoint
Time to solid food tolerance

Secondary Endpoints	
Severe organ failure	Necrosis as determined by CT
Length of hospital stay	Time to medically indicated discharge
Respiratory failure	

CT, computed tomography; CECT/MRI, contrast-enhanced computed tomography; SOC, standard of care; IV, intravenous

Baseline Characteristics Were Generally Aligned Across Groups

Baseline Demographics mITT Population	Placebo N=53	0.5 mg/kg N=52	1.0 mg/kg N=56	2.0 mg/kg N=53
Median Age (Minimum, Maximum)	42 (20, 78)	48.5 (23, 85)	43.5 (22, 84)	42 (19, 91)
Male (%)	33 (62.3)	32 (61.5)	33 (58.9)	33 (62.3)
Female (%)	20 (37.7)	20 (38.5)	23 (41.1)	20 (37.7)
High Hematocrit (% of N) (≥ 44 males, ≥ 40 females)	20 (37.7)	24 (46)	25 (44.6)	23 (43.4)
Any Respiratory Failure (%)	6 (11.3)	4 (7.6)	4 (7.1)	3 (5.6)
Readable Necrotizing Pancreatitis (%)	1/53 (1.9)	4/51 (7.8)	3/56 (5.3)	4/49 (8.1)

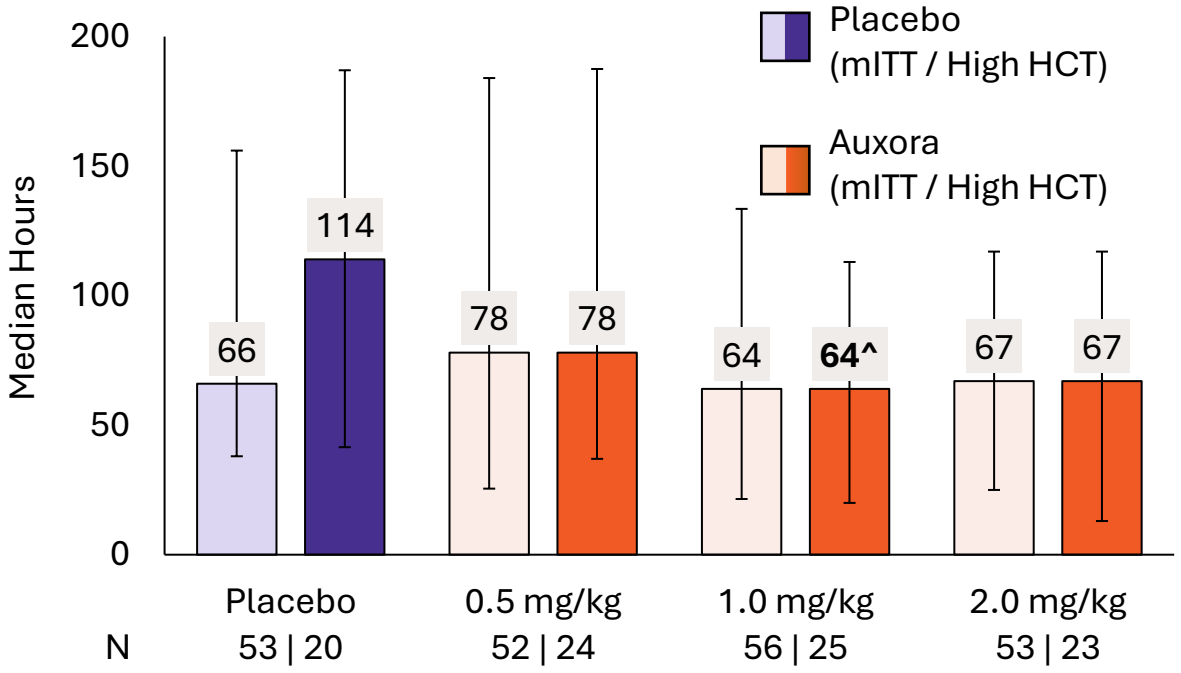
Note: mITT was 214 patients as 2 enrolled patients did not receive study drug

Patients were recruited across 37 sites in both the US and India

mITT, modified intention-to-treat; N, number

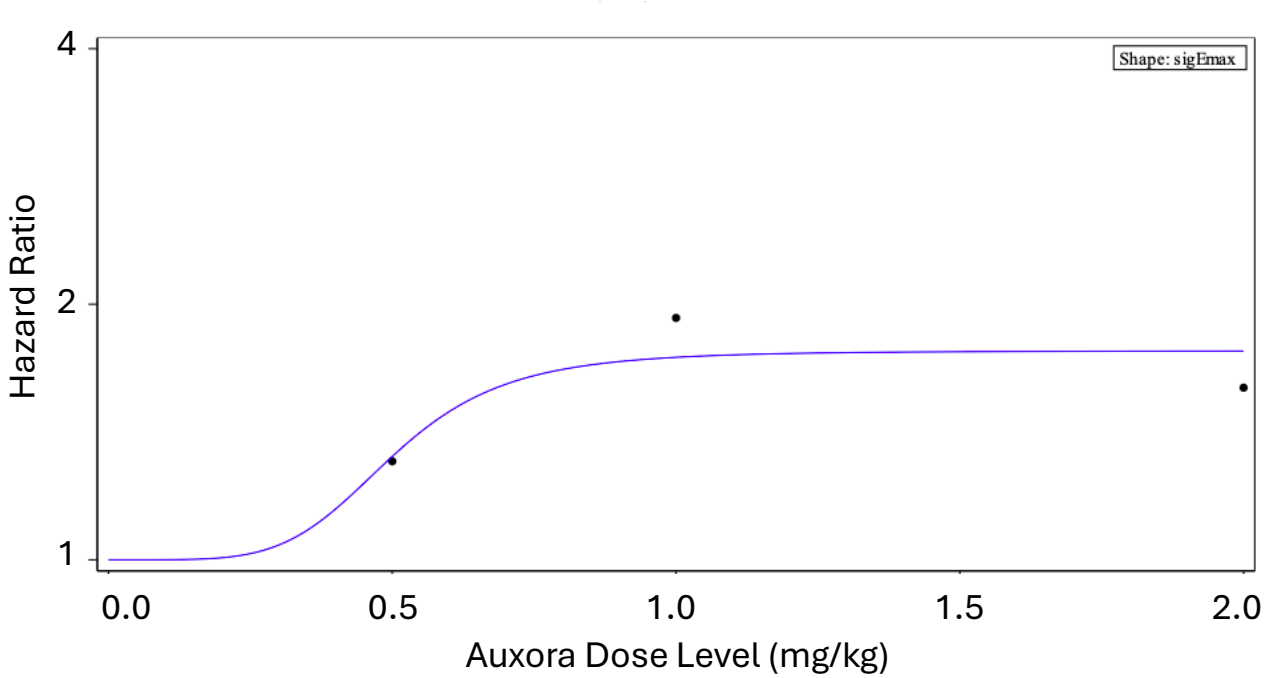
Dose Response Observed for the Primary Endpoint

Time to Solid Food Tolerance mITT Population and Pre-Defined High Hematocrit (HCT) Sub-Group



^p < 0.05 | Error bars represent IQR

gMCP-Mod Analysis Time to Solid Food Tolerance in the High Hematocrit Group



p-value of 0.057 | (The pre-defined α was 0.15)

gMCP-Mod, graph based multiple comparison procedures modified; FDA, US Food & Drug Administration; EMA, European Medicine Agency

Auxora High and Medium-Doses Reduced All Types of Severe Organ Failure

Severe Organ Failure

	Placebo N=53	0.5 mg/kg N=52	1.0 mg/kg N=56	2.0 mg/kg N=53
Respiratory	4/53 (7.5%)	5/52 (9.6%)	2/56 (3.6%)	2/53 (3.8%)
Renal	1/53 (1.9%)	2/52 (3.8%)	1/56 (1.8%)	0/53 (0.0%)
Cardiovascular	1/53 (1.9%)	3/52 (5.8%)	1/56 (1.8%)	1/53 (1.9%)
Any Severe Organ Failure	5/53 (9.4%)	5/52 (9.6%)	2/56 (3.6%)	2/53 (3.8%)

Severe Respiratory Failure: Receiving invasive mechanical ventilation (IMV) OR use of either high flow nasal cannula (HFNC) or non-invasive mechanical ventilation (NIMV) for ≥ 48 hours
Severe Renal Failure: Initiation of renal replacement therapy
Severe Cardiovascular Failure: Use of vasopressor or inotropic support for ≥48 hours

Dose Response was Observed for Both **New Onset** Persistent and Severe Respiratory Failure

Reduced New Onset Persistent Respiratory Failure

	Placebo	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
New Onset Persistent Respiratory Failure	8/47 (17.0%)	5/48 (10.4%)	1/52 (1.9%)	4/50 (8%)

	Placebo + 0.5 mg/kg	1.0 mg/kg + 2.0 mg/kg
New Onset Persistent Respiratory Failure	13/95 (13.7%)	5/102 (4.9%)
Difference		-8.8 %
Relative Reduction		**64.2%**
p-value		**0.0476**

Prevented New Onset Severe Respiratory Failure

	Placebo	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
New Onset Severe Respiratory Failure	4/47 (8.5%)	4/48 (8.3%)	0/52 (0%)	0/50 (0%)

	Placebo + 0.5 mg/kg	1.0 mg/kg + 2.0 mg/kg
New Onset Severe Respiratory Failure	8/95 (8.4%)	0/102 (0%)
Difference		-8.4 %
Relative Reduction		**100%**
p-value		**0.0027**

Respiratory failure:

- P/F ≤300 by arterial blood gas or imputed from pulse oximetry

Persistent respiratory failure was defined as either:

- Severe respiratory failure; OR
- Not Severe: P/F ≤300 for 48 hours, but no use of ventilatory support other than low flow oxygen

Severe Respiratory Failure:

- Receiving invasive mechanical ventilation (IMV); OR
- Use of either high flow nasal cannula (HFNC) or non-invasive mechanical ventilation (NIMV) for ≥ 48 hours

Differences were calculated using Cochran-Mantel-Haenszel test stratified by CRF recorded gender (male or female) and the risk for hematocrit (HCT) (higher or lower) based on CRF data

Auxora High-Dose Demonstrated Improvements in Additional Key Secondary Endpoints within the mITT Population

New Onset Necrotizing Pancreatitis (NP)

	NP At Day 30* (%)	Diff^(%)
Placebo N=53	**17/46 (37.0)**	**-**
0.5 mg/kg N=52	17/44 (38.6%)	1.1%
1.0 mg/kg N=56	20/49 (40.8%)	2.2%
2.0 mg/kg N=53	**11/37 (29.7%)**	**-8.0%**

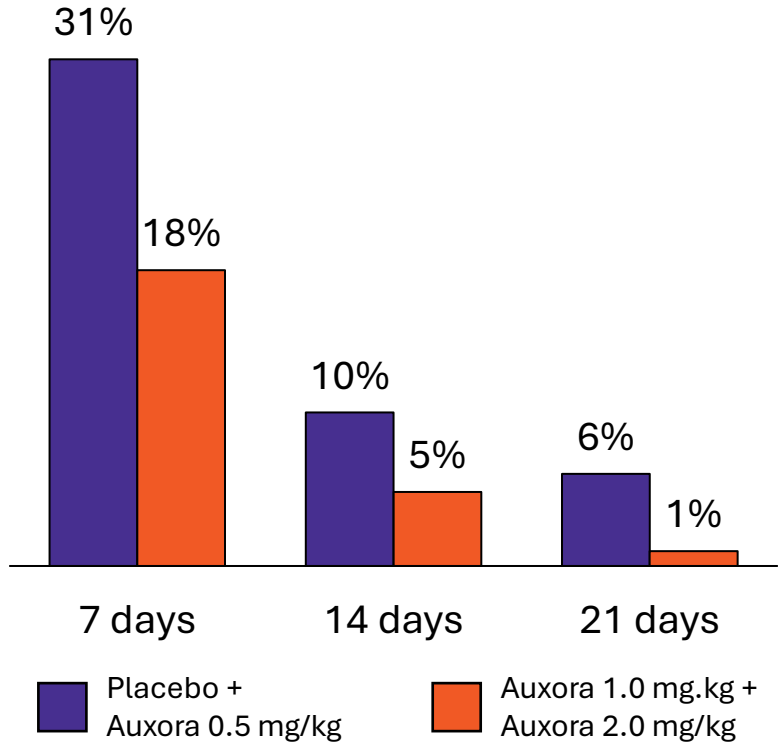
Percentage is based on the number of subjects without Necrotizing Pancreatitis at Screening and non-missing Day 30 Visit or post-treatment unscheduled visit CECT reading results

Time to Medically Indicated Discharge (TMID)

	TMID Median Hours
Placebo N=53	**104.0**
0.5 mg/kg N=52	109.5
1.0 mg/kg N=56	104.5
2.0 mg/kg N=53	**89.0**

TMID defined as: 1) No clinical evidence of infection necessitating continued hospitalization; 2) Solid food tolerance; 3) Abdominal pain has resolved or controlled with medications (non-opiate)

Proportion of Patients Remaining in the Hospital



*If the Day 30 visit data was missing, the last available unscheduled post-treatment data was used for Day 30 analysis based on the LOCF method.
^Cochran-Mantel-Haenszel test stratified by CRF recorded gender (male or female) and the risk for HCT (higher or lower) based on CRF data.

Integration of Key Endpoints into Win Ratio Demonstrates Potential Efficacy of the Auxora High-Dose Compared to Placebo

Win Ratio	All-cause Mortality	New Onset Severe Respiratory Failure	Necrotizing Pancreatitis	Time to Medically Indicated Discharge	Total Wins
Placebo wins	0	0	374	546	920
Auxora 2.0 mg/kg dose wins	0	208	615	730	1553

Stratified Win Ratio: 1.640 | p-value: 0.0372 | 95% CI: 1.030 – 2.612

The win ratio approach provides a comprehensive evaluation of Auxora for AP

- Reduction in respiratory failure will reduce mortality
- Reduction in necrotizing pancreatitis will reduce morbidity
- Reduction in hospital stays will reduce economic burden

CI, confidence internal

Overall Auxora Was Well Tolerated with Few Discontinuations Across all Doses and No Related TESAEs or Deaths for the High Dose Group

Safety Summary: Number of Patients	Placebo N=53	0.5 mg/kg N=52	1.0 mg/kg N=56	2.0 mg/kg N=53
At least one TEAE leading to discontinuation of study drug (%)	3 (5.7)	2 (3.8)	2 (3.6)	2 (3.8)
At least one related TESAE (%)	0	1 (1.9)	0	0
TEAE leading to death (%)	1 (1.9)	0	1 (1.8)	0
At least one TEAE (%)	25 (47.2)	28 (53.8)	36 (64.3)	23 (43.4)
At least one related TEAE (%)	5 (9.4)	9 (17.3)	6 (10.7)	4 (7.5)
At least one TESAE (%)	6 (11.3)	3 (25.0)	12 (21.4)	8 (15.1)

N, total patient population; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse event

The Primary Objective of Dose Response was Achieved While Providing Clinically Meaningful Improvements in Key Outcome Measures

Auxora, a selective CRAC channel inhibitor, provides a novel mechanism of action that inhibits multiple inflammatory pathways in AP

The Phase 2b trial results demonstrate Auxora's potential to reduce mortality and morbidity in AP with SIRs, and provide savings to the healthcare system

- ✓ Dose response observed on primary and across multiple secondary endpoints
- ✓ Positive impact on organ failure, particularly new onset severe respiratory failure
- ✓ Reduction of necrotizing pancreatitis
- ✓ Reduction in time to medically indicated discharge and length of hospital stays
- ✓ Generally well-tolerated

CalciMedica will look to advance Auxora to Phase 3 following meetings with the FDA